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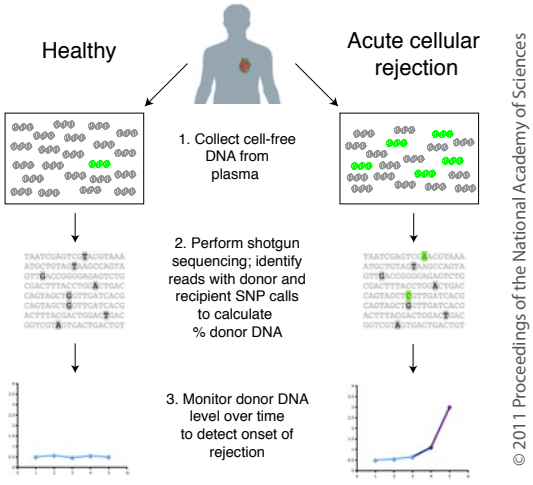
Noninvasive detection of solid-organ transplant rejection

Snyder *et al.*, *Proc Natl Acad Sci USA* 2011; **108**: 6229–6234; doi:10.1073/pnas.1013924108

For most transplanted organs, diagnosis of early rejection requires a biopsy and tissue analysis. However, biopsy of an internal organ is invasive, expensive, causes patient discomfort, and might result in serious complications. Furthermore, analysis of the obtained tissue is limited by sampling error and subjectivity in the analysis of the tissue. Thus, there has been considerable effort to develop noninvasive techniques that might replace or reduce the need for biopsies of transplanted organs. Much of this effort has focused on monitoring the recipient's immune response to detect the onset of rejection. For example, the expression profile of certain genes in peripheral blood mononuclear cells assayed from cardiac transplant recipients has been demonstrated to differ between quiescent patients and those with severe rejection episodes. The AlloMap molecular expression test is the first FDA-approved test based on this research and, when used in conjunction with clinical observation and echocardiograms, has been shown to safely reduce the number of biopsies performed without increasing the risk of serious cardiovascular events. Another noninvasive approach would be, instead of monitoring the recipient's immune response, to directly assay the health of the donated organ. Snyder *et al.* recently reported the development of such an assay by measurement of the signature of dying cells from the organ in the cell-free DNA circulating in the recipient's plasma. They used high-throughput shotgun sequencing (Figure) to develop a universal noninvasive approach to monitoring organ health. They analyzed cell-free DNA circulating in the blood of heart transplant recipients and observed significantly increased levels of cell-free DNA from the donor genome at times when an endomyocardial biopsy independently established the presence of acute cellular rejection. Their results demonstrate that cell-free DNA can be used to detect an organ-specific signature that correlates with rejection. This noninvasive test holds promise for replacing biopsies in solid-organ transplant recipients.

Juan Oliver



General scheme for this study. Cell-free DNA collected in plasma contains a majority of molecules from the recipient (in gray) but may also include some from the transplanted organ (green). Due to increased cell death in the organ during a rejection episode, more donor molecules are expected to be present in the blood at these times. SNP, single-nucleotide polymorphism.

Intravenous erythropoietin in patients with ST-segment elevation myocardial infarction

Najjar *et al.*, *JAMA* 2011; **305**: 1863–1872; doi:10.1001/jama.2011.592

Trials in anemia management in chronic kidney disease have yielded surprising results, demonstrating an increased risk of cardiovascular events associated with the treatment of anemia or treatment targeting higher hemoglobin.[1–3] Thrombocytosis has been theorized as the mechanism. Concurrently, research in animals suggests that following myocardial infarction (MI), animals receiving epoetin alfa had lesser degrees of apoptosis in the infarct area and less reperfusion injury. The REVEAL trial tested the effect of epoetin alfa in patients presenting with an ST-segment elevation MI (STEMI). Patients with STEMIs undergoing emergent percutaneous revascularization underwent randomization to either epoetin alfa or placebo and received the study drug within 4 hours of reperfusion. The first phase of the study randomized a total of 92 patients in a 2:1 ratio to increasing doses of epoetin alfa (15,000, 30,000, or 60,000 units) or placebo. In the second phase, 131 patients were randomized in a 1:1 ratio to 60,000 units of epoetin alfa or placebo. Cardiac magnetic resonance (CMR) imaging was performed within 2–6 days of drug administration and at 12 weeks. The size of infarctions did not differ between treatment arms either on the first CMR scan or on the second CMR scan. However, among patients older than 70 years, the infarct size was larger during the first week in the epoetin alfa group as compared with the group receiving placebo. Additionally, the risk of the composite outcome of death, MI, stroke, or stent thrombosis was greater in the group randomized to epoetin alfa, with events occurring in five patients as compared with zero in the group who received placebo. It is reasonable to conclude that epoetin alfa does not have the same benefit to people experiencing an MI as it does in the preclinical studies. The issue of greater infarct size in the elderly is an important consideration for patients with end-stage renal disease (ESRD). Although the greater risk detected here has not been confirmed in other studies, its potential as a safety signal must be considered carefully. Whether the risk seen with the single large dose of epoetin alfa in this population with normal kidney function may also be seen in patients with ESRD who are treated chronically with epoetin alfa and become acutely ill should be the subject of further consideration, discussion, and research in nephrology.

Lynda Szczech

[1]*N Engl J Med* 1998; **339**: 584–590. [2]*N Engl J Med* 2006; **355**: 2085–2098. [3]*N Engl J Med* 2009; **361**: 2019–2032.

Critical importance of blood pressure level in diabetes

Chen *et al.*, *Hypertension* 2011; **57**: 891–897; doi:10.1161/HYPERTENSIONAHA.110.162446

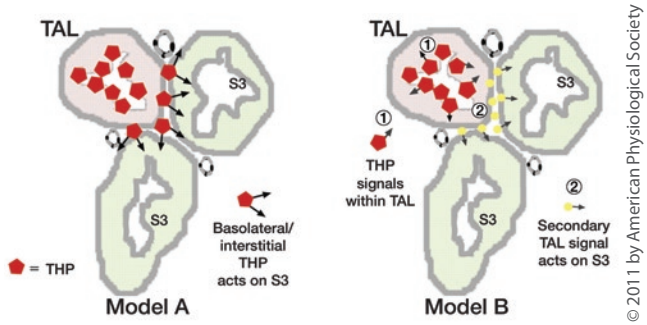
In rich societies, hypertension and diabetes mellitus (DM) are highly prevalent conditions that coexist in many patients. Hypertension is significantly more common in individuals with DM than in the general population, with estimates of the prevalence of hypertension in diabetics ranging from 40% to 80%. DM alone is associated with increased cardiovascular diseases and death, but it is unclear whether this risk is because of the DM per se or because of concomitant hypertension. Indeed, trials of glucose lowering in individuals with DM have reported disappointingly small benefits for myocardial infarction, stroke, or death. Accordingly, Chen *et al.* aimed to determine how much of the risk of cardiovascular disease in individuals with DM might be attributable to hypertension. They retrospectively analyzed prospectively collected data from the Framingham original and offspring cohorts. Of the 1145 Framingham subjects newly diagnosed with DM who did not have a previous history of cardiovascular events, 663 (58%) had hypertension at the time that DM was diagnosed. During 4154 person-years of follow-up, 125 died, and 204 experienced a cardiovascular event. Framingham participants with hypertension at the time of DM diagnosis exhibited significantly higher rates of all-cause mortality and cardiovascular events compared with normotensive subjects with DM. After adjustment for demographic and clinical covariates, hypertension was associated with a 72% increase in the risk of all-cause death and a 57% increase in the risk of any cardiovascular event in individuals with DM. The population attributable risk from hypertension in individuals with DM was 30% for all-cause death and 25% for any cardiovascular event. In contrast, after adjustment for concurrent hypertension, the population attributable risk from DM in Framingham subjects was 7% for all-cause mortality and 9% for any cardiovascular disease event. Thus, although DM was associated with increased risks of death and cardiovascular events, most of this excess risk was attributable to coexistent hypertension. This study further supports the importance of good blood pressure control in patients with diabetes mellitus.

Juan Oliver

Tamm–Horsfall protein-deficient thick ascending limbs promote injury to neighboring S3 segments in an MIP-2-dependent mechanism

El-Achkar *et al.*, *Am J Physiol Renal Physiol* 2011; **300**: F999–F1007; doi:10.1152/ajprenal.00621.2010

Tamm–Horsfall protein (THP) is a glycoprotein exclusively expressed in the kidney, in thick ascending limbs (TALs), and early distal tubules. THP is a defense agent against stone formation and bladder infections, but its role in acute kidney injury (AKI), if any, is not well understood. El-Achkar *et al.* recently described a novel protective role of THP against AKI via downregulation of inflammation in the outer medulla. Their most recent study investigates the mechanistic relationships among the status of THP, inflammation, and tubular injury. Using an ischemia/reperfusion (I/R) model in wild-type and $THP^{-/-}$ mice, the authors demonstrate that the S3 proximal segments, but not the THP-deficient TAL, are the main targets of tubular injury during AKI. The injured S3 segments that are surrounded by neutrophils in $THP^{-/-}$ mice have marked overexpression of the neutrophil chemoattractant macrophage inflammatory protein-2 (MIP-2) as compared with those in their wild-type counterparts. Neutralizing MIP-2 antibody rescues S3 segments from injury, decreases neutrophil infiltration, and improves kidney function in $THP^{-/-}$ mice. Furthermore, using immunofluorescence volumetric imaging of wild-type mouse kidneys, the authors show that ischemia alters the intracellular translocation of THP in the TAL cells by partially shifting it from its default apical surface domain to the basolateral domain, which is contiguous to the basolateral surface of S3 segments. Concomitant with this is the upregulation, in the basolateral surface of S3 segments, of the scavenger receptor SRB-1, a putative receptor for THP. The TAL affects the susceptibility of S3 segments to injury at least in part by regulating MIP-2 expression in a THP-dependent manner.



Possible mechanisms of THP-mediated tubular cross-talk between S3 segments and TAL. Model A: Basolateral/interstitial THP released from the TAL acts directly on S3 segments. Model B: Alternatively, THP affects the TAL, which in turn releases a secondary mediator that acts on S3 tubules. Another possible 'hybrid' mechanism (not depicted here) could involve THP in the interstitium affecting S3 not directly but rather through an effect on interstitial or endothelial cells.

This paper confirms previous findings that neutralization of MIP-2 reduced neutrophil infiltration and susceptibility to kidney injury. The finding of the ischemia-induced translocation of THP in the TAL cells and upregulation of SRB-1 is original and forms a solid foundation for further study of the role of THP in mediating TAL–S3 interactions during injury. Other inflammatory cells that play a role in the process of I/R of the kidney (T cells, macrophages, dendritic cells) should be studied in this model. These interesting findings raise the possibility of a direct role of basolaterally released THP in regulating inflammation in S3 segments (Figure).

Marc De Broe